

Occupational allergic multiorgan disease induced by wheat flour

To the Editor:

Bakers are repeatedly exposed to wheat flour (WF) and may develop sensitization and occupational rhinoconjunctivitis and/or asthma to WF allergens.¹ Several wheat proteins have been identified as causative allergens of occupational respiratory allergy in bakery workers.¹ Testing of IgE reactivity in patients with different clinical profiles of wheat allergy (food allergy, wheat-dependent exercise-induced anaphylaxis, and baker's asthma) to salt-soluble and salt-insoluble protein fractions from WF revealed a high degree of heterogeneity in the recognized allergens. However, mainly salt-soluble proteins (albumins, globulins) seem to be associated with baker's asthma, and prolamins (gliadins,

glutenins) with wheat-dependent exercise-induced anaphylaxis, whereas both protein fractions reacted to IgE from food-allergic patients.¹ Notwithstanding, gliadins have also been incriminated as causative allergens in baker's asthma.²

We report on a 31-year-old woman who had been exposed to WF practically since birth because her family owned a bakery housed in the same home where they lived. She moved from this house when she was 25 years, but she continued working every day in the family bakery. In the last 8 years she had suffered from work-related nasal and ocular symptoms such as itching, watery eyes, sneezing, nasal stuffiness, and rhinorrhea. These symptoms markedly improved when away from work and worsened at work. In the last 5 years, she had also experienced dysphagia with frequent choking, especially when ingesting meats or cephalopods, which had partially improved with omeprazole therapy. Two years before referral to our clinic, she began to have dry cough and breathlessness, which she also attributed to her work environment. Upper and lower respiratory tract symptoms increased when sifting the WF and making the dough. The patient did not experience gastrointestinal symptoms with ingestion of cereal products.

Skin prick test results were positive to grass (mean wheal, 6 mm), cypress (5 mm) and Russian thistle pollen (4 mm), WF (4 mm), and peach lipid transfer protein (6 mm) and were negative to rice flour, corn flour, profilin, mites, molds, and animal dander. Skin prick test with a homemade WF extract (10% wt/vol) was strongly positive (15 mm).

Serologic tests yielded the following results: eosinophil cationic protein, 47 µg/L; total serum IgE, 74 kU/L; specific IgE (ImmunoCAP; ThermoFisher, Uppsala, Sweden) to WF, 7.4 kU/L; barley flour, 1.24 kU/L; and corn, gluten, alpha-amylase, peach, and apple, less than 0.35 kU/L.

Specific IgE binding to microarrayed purified WF allergens (WDAI-0.19, WDAI-0.53, WTAI-CM1, WTAI-CM2, WTAI-CM3, WTAI-CM16, WTAI-CM17, Tri a 14, profilin, ω-5-gliadin, Tri a Bd 36 and Tri a TLP, and gliadin and glutamine fractions) was assessed as described elsewhere.³ The patient's serum specifically recognized ω-5-gliadin and the gliadin fraction, and no IgE reactivity was observed to other wheat allergens. Spirometry revealed a forced vital capacity of 3.88 L (88%), an FEV₁ of 3.04 L (87%), and FEV₁/forced vital capacity of 83%. A methacholine inhalation test was performed following an abbreviated protocol,⁴ and the results were expressed as PD₂₀ in cumulative dose (mg) of methacholine. Methacholine inhalation challenge test result was positive (0.24 mg cumulative dose) when she was working, and after a 3-month period away from work and with no visits to the bakery house, it gave a negative result. A chest x-ray was normal.

Specific inhalation challenge test was carried out in the hospital laboratory by tipping WF from one tray to another for 15 minutes. Spirometry was performed at baseline and at 2, 5, 10, 15, 20, 30, 45, and 60 minutes after the challenge with WF. Peak expiratory flow was measured at baseline and then hourly over 24 hours (respecting sleeping time). A 12% fall in FEV₁ was observed at 20 minutes and a 26% drop in peak expiratory flow at 9 hours after exposure to WF, with respect to baseline values. A control challenge day was performed by exposing the patient to a control substance (normal saline) for 15 minutes, and no significant changes in lung function were observed over a 24-hour observation period.

After 2 months of treatment with omeprazole (40 mg twice a day), an endoscopy with biopsies of 3 sections of the esophagus,

stomach, and duodenum showed macroscopically concentric rings and microscopically more than 70 eosinophils (eos) per hpf in the upper, *middle*, and lower parts of the esophagus. The stomach and the duodenum were normal. Esophagoscopy with biopsy repeated after a 6-week cereal-free diet, but with ongoing exposure to inhaled WF at work, showed persistent eosinophilia (>70 eos/hpf) in the 3 sections of the esophagus.

Esophagoscopy with biopsy after 6 weeks on a diet free of cereals, legumes, milk, egg, nuts, and fish/seafood disclosed more than 60 eos/hpf. Esophagoscopy repeated after the patient had been 6 weeks off work and on a cereal-free diet showed no eosinophils in the esophagus. She was asked to remain away from work but on a diet including cereals, and after 6 weeks no esophageal eosinophils were found. Then, she went back to work, being exposed for 6 weeks to inhalable WF, and eosinophilic esophagitis (EoE) was severely reactivated (>100 eos/hpf).

Increasing evidence supports a link between EoE and environmental aeroallergens in some patients, which can manifest as seasonal exacerbation of EoE.⁵⁻⁷ However, there are no previous reported cases of esophageal disorders by inhalation of cereal flour.

This patient had developed occupational allergic multiorgan disease triggered by IgE-mediated allergy to inhaled WF. A thorough diagnostic workup demonstrated that the changes in respiratory and esophageal outcomes⁸ were work-related. The symptoms and the results of diagnostic tests pointed out that she had developed rhinoconjunctivitis, asthma, and occupational EoE⁹ caused by allergy to gliadin. When she was removed from the workplace, not only asthma symptoms significantly improved but also EoE went into remission, even when she was allowed to eat cereals. Thus, we have ruled out the involvement of cereal ingestion as an eliciting factor of occupational EoE, despite the fact that gliadins are stable to heat and gastric enzymes and exhibit low solubility in gastric and duodenal fluids.¹⁰ Nevertheless, patients with baker's asthma, including those allergic to gliadins, almost invariably tolerate ingestion of cereal products without any ill effect.^{1,2}

In summary, we report the first case of occupational EoE due to WF gliadin triggered by inhalation and not by ingestion, associated with rhinoconjunctivitis and asthma.

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